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The use of health economics to guide drug development decisions: Determining optimal values for an RSV-vaccine in a model-based scenario-analytic approach

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Abstract

Health-economic modelling is useful for assessing the clinical requirements and impact of new vaccines. In this study, we estimate the impact of potential vaccination for respiratory syncytial virus (RSV) of infants in the Netherlands. A decision analysis model was employed using seasonal data from a cohort of children (1996–1997 through 1999–2000) to assess hospitalisation, costs and impact of vaccination. Yearly, an estimated 3670 infants are hospitalised with RSV-infection in the Netherlands, vaccination protecting infants from 3 months of life onwards could prevent approximately 1000–3000 hospitalisations, depending on the effectiveness of the potential vaccine. Additionally, vaccination could prevent a major share of RSV-related costs. Comparison of the calculated break-even prices with the average price of recently introduced vaccines indicates that pricing for a potential RSV-vaccine most likely allows for only a single dose vaccination or several doses at a relatively low price per dose in order to achieve cost savings. However, if evidence on relevant RSV-related mortality would become available, higher pricing would be justified, while still remaining below accepted thresholds for cost-effectiveness.

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Keywords: Health economics; RSV; Vaccination

1. Introduction

Human respiratory syncytial virus (RSV) infection is the most important cause of viral respiratory tract infection in infants. RSV causes upper and lower respiratory tract infection and can lead to pneumonia or bronchiolitis [1,2]. It is estimated that every child at the age of two has been infected at least once with RSV [3]. The epidemiology of RSV in northern regions with temperate

climates is characterized by seasonality, with almost all cases occurring between October and April [1,2]. Severe RSV-infection with hospitalisation occurs in approximately 0.5–2% of the infected infants [3]. Prematurely born infants and infants with congenital heart disease (CHD) and bronchopulmonary disease (BPD) are at increased risk for severe RSV-disease. The American Academy of Pediatrics (AAP) recommends RSV-prophylaxis during the RSV-season for infants with lung and heart diseases and those born prematurely [4]. Primary prophylaxis may be achieved by administering either palivizumab or RSV-immunoglobulin. However, approximately 80% of RSV-infections occur out-

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side these known high-risk groups, implying that despite prophylaxis RSV still remains a significant source for morbidity.

Although mortality may be relatively low for RSV-infection, the impact on quality of life of both the child and its parents is potentially large [5]. Also, due to the high incidence of RSV-infection in infants, costs and burden of illness for society may be substantial, especially when the costly treatment with palivizumab or immunoglobulin as secondary prophylaxis to prevent severe RSV-disease is taken into account [6]. Next to infections of the respiratory tract, RSV infection is also suspected to be a major cause of otitis media, which is one of the most frequently occurring diseases in childhood [7]. RSV-infection is additionally associated with recurrent episodes of wheezing [8], which may lead to increased costs of care and a reduced quality of life. One further issue concerns the identification of RSV-infection. In particular, the infection is often conceived and classified as influenza, leading to potentially large underestimation of the real burden of RSV [9]. On the other hand, the recently discovered human metapneumovirus (hMPV) causes respiratory tract infections in infants and children with symptoms very similar to those of RSV-infection and hence hMPV-infections may be occasionally mistaken for RSV, thus causing a slight overestimate of the RSV incidence [10,11].

In the light of burden of disease, the potential for underdiagnosis, and the low efficacy of the possible prophylactic regimens, ideally a vaccine should be available that actively protects infants and children at risk and reduces transmission of the virus. Until now, however, there is no effective vaccine against RSV-infection available. Yet, some early phase trials are going on. A major setback in the development of RSV-vaccines has been the unfortunate experience with formalin-inactivated RSV-vaccine formulations (FI-RSV) in the 1960s. This FI-RSV was administered to infants and children in the USA. Upon subsequent exposure to live virus in the winter season of 1966–67, several of these vaccinated children developed enhanced disease and two vaccinated children even died as a result of RSV-infection. Despite numerous studies into the basis of vaccine-induced severe RSV-disease, it is still not entirely clear what the immunological correlates of the observed enhanced RSV-pathology are. Currently, there are two types of candidate vaccines in clinical evaluation: live-attenuated for vaccination of primarily RSV-seronegative young infants, and inactivated subunit formulations for vaccination of the elderly and RSV-seropositive children at risk for severe RSV-disease and pregnant women [12–14]. A difficulty but – given the epidemiology – yet important requirement for a successful vaccine against RSV-infection in children would be the ability of such a vaccine to safely induce protective efficacy at a very early age.

Health-economic modelling can be used to assess the impact of future preventive and therapeutic strategies and to estimate threshold values for important characteristics such as efficacy and price. Vaccine characteristics, such as the abil-

ity to induce protective immunity and reduce transmission of the virus, are at least partly determined by the exact vaccine formulation (inclusive the use of an adjuvant) and the route of vaccine administration. The use of an appropriate model may even allow us to estimate the exact optimal timing of vaccination in close conjunction with these specific vaccine characteristics. The results of the model may thus contribute to decisions regarding timing of vaccination and the associated price of the vaccine [15].

Outputs of a health-economic model are important for policy makers of national immunization schedules to provide epidemiological output on morbidity averted, cost-effectiveness output and budget impact, all necessary components in a planning of future additions to National Immunization Programs. Furthermore, the model may produce break-even vaccine prices where financial benefits outweigh the vaccine costs, providing additional information on the expected willingness to pay for the vaccine and hence on the expected returns on investment and feasibility of the efforts. This information may in turn influence decisions on the funding of RSV-vaccine research programs. Summarizing, knowledge of the impact of vaccine parameters such as price and minimum efficacy may crucially contribute to decisions regarding vaccine development and future use of the vaccine in National Immunization Programs.

In this paper, a health-economic model is presented simulating RSV-vaccination of infants in The Netherlands. In particular, scenarios for various values of effectiveness and timing of potential vaccination are made, seasonal patterns are investigated and break-even costs for vaccination are analyzed. The model allows calculation of cost-effectiveness per life-year gained, however the scarcely available Dutch data indicate no case fatalities for RSV in Dutch infants. In the absence of Dutch data on mortality for RSV-infected children, in the discussion part of this paper some further tentative analysis is performed on USA-data on mortality. This allows the specification of acceptable costs of the potential vaccine with regard to thresholds for the cost per life-year gained that have recently been suggested for the Netherlands. As such, this paper illustrates the use of pharmacoeconomic models at an early stage of drug or vaccine development, whereas the majority of papers published in the field yet relate to the post-marketing phase of a vaccine in the framework of reimbursement decisions.

2. Methods

2.1. Health-economic model

We developed a health-economic model for RSV-vaccination directed at children without BPD (it was assumed that BPD-infants would be vaccinated without any discussion if an RSV-vaccine became available given the high level of risk for these infants). The costs and effects of RSV-vaccination of non-BPD infants were assessed in a cohort

model, following a birth cohort twice: once without vaccination and once with vaccination at assumed plausible values for effectiveness and period of protection. The size of the birth cohort in the Netherlands is approximately 200,000. This cohort is subject to probabilities for hospitalisation due to RSV within a cycle length of the model of 1 month. So, the model is evaluated on a monthly basis; i.e. during any month the cohort faces specific probabilities for RSV-hospitalisation. Such transition probabilities and costs of hospitalisation were derived from a retrospective population-based study, conducted in the South-west of the Netherlands [16,17]. The time horizon of the model was limited to 24 months (after birth), as it has been found that nearly all RSV-hospitalisations in children occur in this period. The model thus effectively limits the duration of protection of vaccination to a time period of maximally 24 months after vaccination. The net costs were defined as the costs of the vaccination programme minus the savings on health-care costs for severe RSV-infections. Costs of hospitalisation were modelled using a regression model based on the retrospective population based study. Non-hospital costs were derived from another source (see below). All costs were expressed in 2003 price levels.

2.2. Retrospective population-based study

In the retrospective population-based study, data on risk factors and hospital resource use was gathered from all children with an RSV-related hospitalisation in one of the 29 regional hospitals in the South-west of the Netherlands during four consecutive RSV-seasons 1996–1997 through 1999–2000 [16]. In this region, approximately 47,000 infants are born annually. Of these cohorts, 3458 were hospitalised for RSV during the whole period. Table 1 presents the patient characteristics. Detailed information for these patients on level of care, diagnostics and medical interventions was gathered from medical records. Resource use was transformed into costs using unit prices including accommodation, overhead, nondisposable equipment, personnel and disposables [16]. Time and equipment needed was estimated through questionnaires among caregivers [16]. In the end, all RSV-hospitalisations could be labelled with a cost estimate (price-level 2000; updated for this study to 2003).

With these data, a linear regression model was developed with hospitalisation costs as the outcome. This model enabled forecasting hospitalisation costs based on risk factors including gestational age, birth weight and BPD. The regression model has been extensively described in the literature by Rietveld et al. [17]. For our study the regression model for non-BPD infants was used, forecasting hospitalisation

Table 1

Characteristics of the cohort of children hospitalised with proven RSV-infection during RSV-seasons 1996–1997 to 1999–2000 [16]

Characteristic	Number	Percentage
Gender		
Male	2031	58.7
Female	1427	41.3
Gestational age (weeks)		
<28	50	1.4
29–30	39	1.1
31–32	67	1.9
33–34	139	4.0
35–36	238	6.9
>37	2924	84.6
Birth weight		
≤2500	533	15.4
2501–3000	625	18.1
3001–3500	1124	32.5
3501–4000	825	23.9
>4000	351	10.2
BPD		
Yes	54	1.6
No	3404	98.4
Age of RSV diagnosis		
0	165	4.8
1–3	1569	45.4
4–6	866	25.0
>6	858	24.8

costs at:

$$2274 + 1226 \times \text{ga1} + 313 \times \text{ga2} + 591 \times \text{bw1} + 284 \times \text{bw2} + 2192 \left(\frac{1}{\text{age} + 1} \right) \quad (1)$$

with ga1 = gestational age ≤28 weeks; ga2 = gestational age from 29 to 34 weeks; bw1 = birth weight ≤2500 g; bw2 = birth weight from 2501 to 3000 g; age = age in months (the term $1/(\text{age} + 1)$ was included to stabilise variance [17]). This implies that in the model hospital costs vary by age, gestational age and birth weight: theoretically, from just over €2300 to a maximum of €6283.

Previously, a subset of the patients in Table 1 (seasons 1996–1997 through 1998–1999) was used to estimate the risk of being hospitalised for RSV, based on population-based risk factors [15]. Risk factors considered for non-BPD infants were selected from the literature and included the same as mentioned above (gestational age, birth weight and age) in addition to gender and month of the year (reflecting seasonality of RSV). The following prediction rule for the monthly RSV-hospitalisation risk was specified for non-BPD children during the RSV-season (October through April; for other months the expected number of RSV-hospitalisations is 0):

$$\frac{1}{1 + \exp(7.013 - 0.335 \times \text{gender} - 0.545 \times \text{bw1} - 0.234 \times \text{bw2} - 1.150 \times \text{ga1} - 1.042\text{ga2}' - 0.849 \times \text{ga3} - 0.447 \times \text{ga4} - 1.398 \times \text{aged} + 0.207 \times \text{age} - 0.851 \times s)} \quad (2)$$

with $ga1$ = gestational age ≤ 28 weeks; $ga2'$ = from 29 to 32 weeks; $ga3$ = 33 or 34; $ga4$ = 35 or 36; $bw1$ = birth weight ≤ 2500 g; $bw2$ = birth weight from 2501 to 3000 g; age = age in months;¹ $aged$ = 0 if age = 0, $aged$ = 1 otherwise; s reflects the seasonal factor at -1.40 for October, 0.53 for November, 1.36 for December, 0.83 for January, 0.53 for February, -0.22 for March and -1.63 for April. The regression models have been validated previously [16,17]. Overall goodness of fit of both models was satisfactory, as indicated by an R^2 of 0.85 for the cost model and a non-significant Hosmer–Lemeshow test ($p = 0.79$) for the risk model [16,17].

2.3. Cohort model

The resulting regression models were used as input for the cohort model in which infants born in a specific month were followed for 24 months. The model simulates the risk of children becoming hospitalized due to RSV infection using formula (2). For this purpose, the monthly numbers of children born in 2003 (maximum: 17,000 in July and August; minimum: 15,000 in February; source: Central Bureau of Statistics Netherlands) were taken and the risks estimated from the regression models were used to assess the actual number of children hospitalised. It was assumed that 99% of the infants were non-BPD children [16,17]. Distributions of gestational age and birth weight of the monthly birth cohorts were also based on the information on the annual birth cohorts followed by Rietveld et al. [16,17].

In the next step of the model, corresponding costs of hospitalisations were calculated using formula (1). In the model hospital costs were inflated to reflect 2003 price levels using appropriate deflators [18]. Based on a study on societal costs of RSV-infection in infants in the Netherlands, it was assumed that hospital costs reflected 87% of all societal costs related to a severe RSV-episode [19]. In particular, additional costs arise for GP-visits, home care and work loss of parents [19]. Furthermore, discounting at 4% was applied to costs for children aged 12 months and over [18].

The model was once evaluated without vaccination; i.e. the natural course of infections as has been observed in the study by Rietveld et al. [16,17]. Then, the model was evaluated assuming a vaccination with a specific effectiveness achieved (% infections/hospitalisations prevented), a specific starting month of such protection (immediately in the first month after birth is the earliest theoretical option) and specific vaccination costs, i.e. vaccine price plus administration costs (the latter are €6.2 in the Netherlands [20]). Each combination of effectiveness and first month of life with protection forms a specific scenario. Note that effectiveness and starting month of protection are specified, we do not specify the exact moments for vaccination. If, for example, the first month of

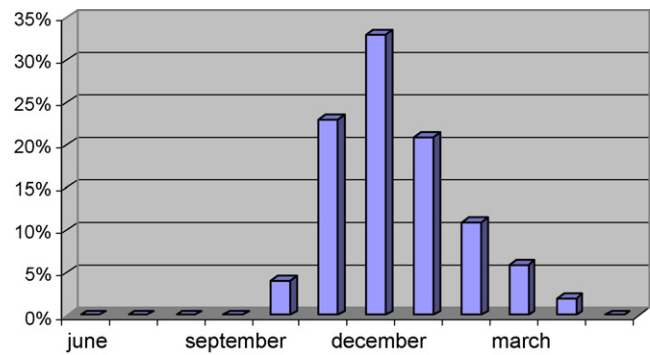


Fig. 1. Percentage distribution of RSV-hospitalisations in the Netherlands (source: [16,17]).

protection is the third month of a child's life, we implicitly assume that vaccination is performed prior to that month (i.e. in months 1 and 2).

As outcomes in our scenarios two entities were chosen: (i) break-even costs of vaccination and (ii) net costs per hospitalisation averted. Mortality nor life-years gained were included in the model. In fact, no fatal RSV-infections were observed in the Dutch retrospective research outlined above [16,17]. Also, impacts in terms of quality of life or the effects on the occurrence of long term effects (i.e. wheezing) were not included at this stage of the research.

During the period of analysis, RSV-infection (as is common in Northern climates) followed a highly seasonal pattern, with infections occurring between October and April (Fig. 1). Since risks are also highly depending on age (younger infants are more susceptible for RSV-infection; Fig. 2), the risk of becoming hospitalised for RSV and correspondingly the absolute efficacy of RSV-vaccination, will depend on the date of birth of the infant in relation to the RSV-season (just prior to the RSV-season or not). As a consequence, the cost-effectiveness of RSV-vaccination will shift throughout the season. To account for this, we also present the results of the model for all months of birth separately; in particular, cost-effectiveness was estimated monthly in terms of net costs per hospitalisation averted.

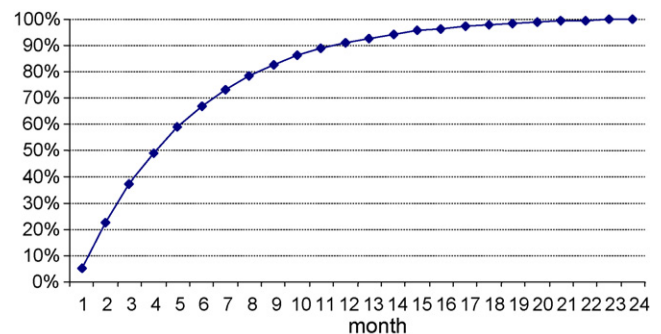


Fig. 2. Cumulative distribution of cases of RSV according to month of life (source: [16,17]).

¹ For premature infants, age was corrected to a duration of pregnancy of 38 weeks [17].

Table 2

Number of RSV related hospitalisations averted for a birth-cohort of Dutch infants for a range of vaccine effectiveness and start of protective immunity by month of life (95% confidence intervals are shown between brackets)

Effectiveness (%)	Start protective immunity (month of life)					
	1	2	3	4	5	6
50	1760(1010–3010)	1430(790–2610)	1170(640–2050)	950(550–1900)	770(410–1400)	620(330–1120)
60	2110(1090–3750)	1720(1020–2880)	1400(790–2320)	1140(660–2080)	920(520–1620)	740(430–1320)
70	2460(1430–4120)	2010(1130–3510)	1630(960–2700)	1330(780–2360)	1070(610–1960)	860(480–1470)
80	2820(1610–4830)	2300(1360–3860)	1870(1030–3240)	1520(880–2540)	1230(670–2050)	990(510–1960)
90	3170(1810–5450)	2580(1460–4500)	2100(1160–3560)	1710(950–2860)	1380(780–2560)	1110(610–1960)
100	3520(2130–5800)	2870(1700–5340)	2340(1220–4030)	1900(1080–3410)	1530(850–2720)	1230(670–2110)

2.4. Probabilistic sensitivity analysis

Statistical uncertainty was assessed with multivariate probabilistic sensitivity analysis using Monte Carlo simulation with normal distributions for the parameters in both regression models [21], with the means as specified in formulas (1) and (2) and standard deviations derived from the same data (available on request). Monte Carlo simulation thus enables specification of the uncertainty intervals for cost-effectiveness (in particular, 10,000 simulations were performed to derive the 95% uncertainty interval using @RISK 4.5 software).

3. Results

The annual number of RSV-related hospitalisations in Dutch children is estimated at 3670 (95% CI: 2160–6290), costing on average €14,170,400 per year (average costs per case: €3860).

Hospital costs are estimated to account for the largest burden of costs at €12,328,200. Non-hospital costs due to GP-visits, work loss of parents and traveling fees amounted up to approximately €1,842,200.

The impact of the exact first month of protective immunity on the number of cases of severe RSV-infections that require hospitalisation was assessed for a range of vaccine effectiveness from 50 to 100% and different first months of protection. The results are presented in Table 2. For 70% effectiveness, a vaccine that offers protective immunity to infants aged from 3 months onwards would decrease the number of RSV-hospitalisations with approximately 1630

cases per year. A vaccine with 90% effectiveness and protective immunity from 3 months onwards would result in an annual decrease of approximately 2100 cases of RSV-infection.

An indication of the acceptable vaccine price for policy makers could be made by calculation of the break-even costs for vaccination (i.e. costs per vaccination so that the costs of vaccination are fully offset by the financial benefits of averting hospitalisation due to RSV). For a vaccine with a 70% effectiveness and protective immunity from month 3 onwards, these corresponding break-even costs would be €29 (95% CI: €17–50). A vaccine with 90% effectiveness and again protective immunity from 3 months onwards would yield break-even costs at €38 (95% CI: 21–69). In Table 3, the break-even costs for the RSV-vaccine are shown as a function of effectiveness and month of start of protection. One way to interpret this Table is to consider one break-even price – say €26 – and find those combinations of effectiveness and protective immunity that correspond to this price (in this case from 50% effectiveness and protective immunity from 2 months onwards up to 100% effectiveness and immunity from 5 months onwards).

As indicated above, RSV-infection follows a highly seasonal pattern, with most infections occurring between October and April. As a result of this seasonality, vaccination of infants born in or just prior to the RSV-season would yield optimal benefits. Thus, it could be worthwhile to only vaccinate those infants born prior to the start of the RSV-season. This is shown in Fig. 3, which indicates the costs per hospitalisation averted as a function of month of birth. We have chosen here again for presenting results of a vaccine with 70% effectiveness and protective immunity from 3

Table 3

Break-even costs (€) (vaccine price and administration costs) per vaccinated infant for a range of vaccine effectiveness and start of protective immunity by month of life (95% confidence intervals are shown between brackets)

Effectiveness (%)	Start protective immunity (month of life)					
	1	2	3	4	5	6
50	34(18–61)	26(14–45)	21(11–37)	17(10–31)	13(7–24)	11(6–18)
60	41(23–70)	32(17–56)	25(15–46)	20(12–37)	16(9–29)	13(7–23)
70	47(24–77)	37(22–65)	29(17–50)	23(13–44)	18(11–33)	15(8–27)
80	54(29–91)	42(26–69)	33(20–59)	27(16–48)	21(12–40)	17(9–29)
90	61(33–102)	47(26–86)	38(21–69)	30(17–52)	24(13–48)	19(10–35)
100	68(47–115)	53(30–97)	42(23–72)	33(18–60)	26(14–48)	21(12–38)

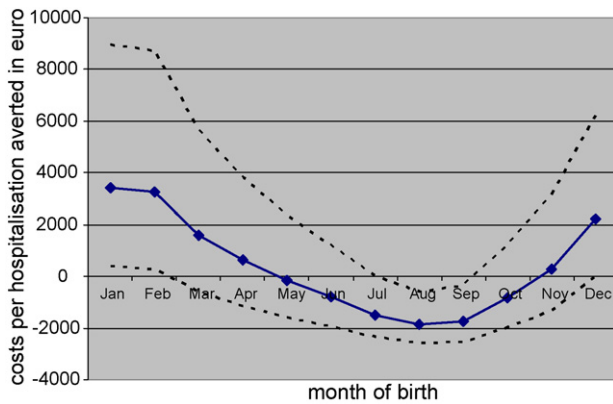


Fig. 3. Costs per hospitalisation due to RSV averted for infants born in different months, for a vaccine with 70% effectiveness and protection from 3 months onwards and vaccination costs at €26, with 95% CIs indicated by the dotted lines (to show the full curve also negative costs per hospitalisation are included; note that the exact values of these negative ratios may not be meaningful; negatives merely show that we encounter the 'desirable' situation of net cost savings combined with hospitalisations being averted).

months onwards. For the vaccine costs we chose €26, corresponding to a theoretical one-dose vaccination with a vaccine price of €20 plus administration costs of approximately €6 or various subsequent vaccinations in the first months of life at very low vaccine costs. The results are dependent on the time of birth of the infant in relation to the RSV-season. To illustrate this, the costs per hospitalisation averted for infants born in January are approximately €3400, whereas vaccination of infants born between June and September would be cost-saving.

4. Discussion & conclusion

In this analysis, we have calculated the impact of a potential vaccine against RSV-infections for a number of scenarios. One of the main purposes of this analysis was to establish minimum values for both the effectiveness of the vaccine and the timing of vaccination. Information on these crucial vaccine parameters could be used to drive strategic research decisions with regard to the development of such a vaccine. For instance, a vaccine that needs to be administered shortly after or even prior to the partus would require a different research and development path than a more conventional vaccine. Also, the analysis provides strategic information for policy makers working on future developments of national vaccination programs in different countries. It provides information on the possible public-health effects of the intervention, as well as the associated costs of including RSV-vaccination in a National Immunization Program. This would enable policy makers to allocate budgets for such a vaccine upfront.

In the Netherlands, annually approximately 3670 hospitalisations in infants occur due to RSV-infection. Universal infant vaccination with a vaccine that induces protective

immunity in infants from 3 months onwards would avert approximately 1000–3000 hospitalisations, depending on the effectiveness of the vaccine. The break even price for vaccination would lie approximately between €20 and 50, depending again on vaccine effectiveness. As an example, a vaccine that offers protective immunity to infants from the second month of life onwards would prevent between 1430 and 2870 RSV-hospitalisations, resulting in higher break-even costs for the vaccination of between €26 and €53. Of course, the market value of such a vaccine is not only dictated by the break-even price of vaccination, also aspects such as willingness to pay of parents or health-care authorities for prevention of RSV-infection among infants should be taken into consideration and may increase the prices as specified in this paper several fold. Additionally, we note that one further aspect for pricing relates to the complexity of developing this vaccine and thus the costs of the research and development necessary to bring this vaccine to fruition; costs that are not included explicitly in our analysis. Finally, we note that any potential downside costs of vaccination, which might include medical visits if the vaccine had febrile side effects and relevant costs of any more serious adverse effects, were not included in our model.

Break-even values most likely correspond with a one-off vaccination (instead of several subsequent doses), since recently introduced vaccines on average cost €40 per dose (Mercer management consulting, personal communication). Also, the results indicate that full protection would be needed in infants as early as possible, which also points in the direction of a single shot vaccine given prior to the 2nd or 3rd month of life. In the absence of a fully characterized RSV-vaccine, it is not yet clear whether this is technically feasible. Additionally, we showed a variation in cost-effectiveness regarding the seasonal timing of vaccination. This could induce a recommendation to vaccinate seasonally, for example, preferably prior to the RSV-season. However, given the Dutch practice within the infant National Immunization Program – which is of course universal rather than seasonal – such a seasonal vaccination might be difficult to implement, although a successful example does exist for elderly seasonal influenza vaccination.

Our model was limited to children without BPD. Inclusion of children with BPD would have highly complicated our health-economic model. Children with BPD only involve a small group (approximately 1% of all RSV-hospitalisations). Furthermore, one might expect that due to the relatively high risk for severe RSV-disease in this group, less discussion on vaccination for this small group might be expected, vaccination is highly likely to be cost saving and will only have a very limited budget impact.

This analysis of health effects of RSV-vaccination takes only hospitalisations due to RSV into account. However, a large number of RSV-infections in infants does not require hospitalisation, and follows a similar clinical pathway as other respiratory illnesses (for example, as of influenza). These infections may cause significant burden for society due to work loss caused by parents for taking care of the ill infant.

In our analysis, the effects of vaccination on these milder RSV-infections are not incorporated, causing an underestimation of the health effects of vaccination and the associated break-even costs for vaccination. Also, impacts in terms of quality-of-life due to complications of RSV in later life (for example, wheezing) have not been evaluated in our current work; further work should be directed towards those impacts. Finally, we note that we did not find fatal cases of serious RSV-infections in our retrospective epidemiological research [16,17]. Thompson et al. did however estimated relevant mortality due to RSV for the United States, using regression models on national mortality and respiratory virus surveillance data [22]. This may indicate that further data gathering in the Netherlands might also reveal relevant mortality due to RSV, and inclusion of this in the cost-effectiveness analysis may enhance cost-effectiveness of the potential vaccine.

If one would assume some modest mortality figures in the range of 4–8 cases annually [22–24], some crude cost-effectiveness estimates could be made. In particular, threshold vaccine costs could be estimated at which net costs per life-year gained equal the informal Dutch cut-off at €20,000 per discounted life-year gained (discount rate at 1.5% for life-years according to the Dutch guideline) [25,26]. For example, for a vaccine efficacy of 70% and protective immunity provided from the age of 3 months onwards, threshold vaccine costs would then range from €50 to 75. Recently higher cost-effectiveness thresholds have been suggested for the Netherlands [27], allowing even much higher vaccination costs over €100. Ergo, further research is needed into the mortality of RSV among infants and its results would crucially influence the exact levels of acceptable threshold vaccination costs.

We conclude that in the Netherlands, annually approximately 3670 hospitalisations in infants occur due to RSV infection. A vaccine could prevent a major share of these; as early as possible vaccination after birth is crucial in this respect. For breakeven, total vaccination costs related to such a vaccine would nevertheless not be allowed to be over approximately €50. However, if further evidence on mortality among infants with RSV would come out and warrant inclusion into a cost-effectiveness framework, indeed pricing over €50 upto above €100 would become feasible, based cost-effectiveness thresholds. With this model, we demonstrate the potential value of health-economic modelling to assist in R&D-decisions, in this case enabling rational weighting of the benefits and pricing of vaccination versus R&D-investments required.

References

- [1] Hoffman SJ, Laham FR, Polack FP. Mechanisms of illness during respiratory syncytial virus infection: the lungs, the virus and the immune response. *Microbes Infect* 2004;6(8):767–72.
- [2] Shay DK, Holman RC, Newman RD, Liu LL, Stout JW, Anderson LJ. Bronchiolitis-associated hospitalizations among US children, 1980–1996. *JAMA* 1999;282(15):1440–6.
- [3] Henderson FW, Collier AM, Sanyal MA, Watkins JM, Fairclough DL, Clyde WA, et al. A longitudinal study of respiratory viruses and bacteria in the etiology of acute otitis media with effusion. *N Engl J Med* 1982;306(23):1377–83.
- [4] American Academy of Pediatrics; Committee on Infectious Diseases and Committee on Fetus and Newborn. Revised indications for the use of palivizumab and respiratory syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infections. *Pediatrics* 2003;112:1442–6.
- [5] Bont L, Steijn M, van Aalderen WM, Kimpen JL. Impact of wheezing after respiratory syncytial virus infection on health-related quality of life. *Pediatr Infect Dis J* 2004;23(5):414–7.
- [6] Paramore LC, Ciuryla V, Ciesla G, Liu L. Economic impact of respiratory syncytial virus-related illness in the US: an analysis of national databases. *Pharmacoeconomics* 2004;22(5):275–84.
- [7] Klein JO. The burden of otitis media. *Vaccine* 2000;19(Suppl. 1):S2–8.
- [8] Henderson J, Hilliard TN, Sherriff A, Stalker D, Shammari NA, Thomas HM, et al. Hospitalization for RSV bronchiolitis before 12 months of age and subsequent asthma, atopy and wheeze: a longitudinal birth cohort. *Pediatr Allergy Immunol* 2005;16:386–92.
- [9] Zambon MC, Stockton JD, Clewley JP, Fleming DM. Contribution of influenza and respiratory syncytial virus to community cases of influenza-like illness: an observational study. *Lancet* 2001;358(9291):1410–6.
- [10] van den Hoogen BG, de Jong J, Groen J, Kuiken T, de Groot R, Fouchier RAM, et al. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. *Nat Med* 2001;7:719–24.
- [11] Van den Hoogen BG, Osterhaus ADME, Fouchier RAM. Clinical impact and diagnosis of human metapneumovirus infection. *Pediatr Infect Dis J* 2004;23:S25–32.
- [12] Dudas RA, Karron RA. Respiratory syncytial virus vaccines. *Clin Microbiol Rev* 1998;11:430–9.
- [13] Durbin AP, Karron RA. Progress in the development of respiratory syncytial virus and parainfluenza virus vaccines. *Clin Infect Dis* 2003;37(12):1668–77.
- [14] Polack FP, Karron RA. The future of respiratory syncytial virus vaccine development. *Pediatr Infect Dis J* 2004;23(Suppl. 1):S65–73.
- [15] Bos JM, Alphen Lv., Postma MJ. The use of modeling in the economic evaluation of vaccines. *Expert Rev Pharmacoeconomics Outcomes Res* 2002;2(5):443–55.
- [16] Rietveld E, de Jonge HCC, Polder JJ, Vergouwe Y, Veeze HJ, Moll HA, et al. Anticipated costs of hospitalization for respiratory syncytial virus infection in young children at risk. *Pediatr Infect Dis J* 2004;23(6):523–9.
- [17] Rietveld E, Vergouwe Y, Steyerberg EW, Huysman MWA, de Groot R, Moll HA. Respiratory syncytial virus hospitalisation in young children: development of a clinical prediction rule. *Pediatr Infect Dis* 2006;25:201–7.
- [18] College voor Zorgverzekeringen (CvZ). Guideline prices for pharmacoeconomic research. Diemen: CvZ; 2004.
- [19] Miedema CJ, Kors AW, Tjon a Ten WE, Kimpen JLL. Medical consumption and socioeconomic effects of infection with respiratory syncytial virus in the Netherlands. *Pediatr Infect Dis J* 2001;20(2):160–3.
- [20] Bos JM, Rumke H, Welte R, Postma MJ. Epidemiologic impact and cost-effectiveness of universal infant vaccination with a 7-valent conjugated pneumococcal vaccine in the Netherlands. *Clin Ther* 2003;25:2614–30.
- [21] Altman DG. Practical statistics for medical research. London: Chapman and Hall; 1991.
- [22] Thompson WW, Shay DK, Weintraub E, Brammer L, Cox N, Anderson LJ, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA* 2003;289:179–86.
- [23] Fleming DM, Pannell RS, Cross KW. Mortality in children from influenza and respiratory syncytial virus. *J Epidemiol Community Health* 2005;59:586–90.

- [24] Fleming DM, Pannell RS, Elliot AJ, Cross KW. Respiratory illness associated with influenza and respiratory syncytial virus. *Arch Dis Child* 2005;90:741–6.
- [25] Klok RM, Brouwer WBF, Annemans LA, Bos JM, Postma MJ. Towards a healthier discount procedure. *Expert Rev Pharmacoeconomics Outcomes Res* 2005;5:59–63.
- [26] Bos JM, Postma MJ. Using pharmacoeconomics for policy making: is rational decision making enhanced by applying thresholds for cost-effectiveness? *Expert Rev Pharmacoeconomics Outcomes Res* 2004;4:247–50.
- [27] Raad voor de Volksgezondheid en Zorg (RVZ). *Zicht op Zinnige en Duurzame Zorg*. The Hague: RVZ (Netherlands); 2006.